Project Title: Functional Imaging of Tremor Circuits and Mechanisms of Treatment Response

Principal Investigator: Fatta Nahab M.D., Associate Professor of Neurosciences, University of California San Diego

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 05/11/2011

1. PROJECT TITLE

Functional Imaging of Tremor Circuits and Mechanisms of Treatment Response

2. PRINCIPAL INVESTIGATOR

Fatta B. Nahab, M.D.

3. FACILITIES

University of California San Diego
Department of Neurosciences
Functional Imaging of Neurodegenerative Disorders Lab
Center for Translational Imaging and Personalized Medicine
Keck Center for Functional Magnetic Resonance Imaging (CFMRI), UCSD
Clinical and Translational Research Institute, (CTRI), UCSD

4. ESTIMATED DURATION OF THE STUDY

The estimated duration of this study is 5 years for subject recruitment, fMRI testing, data analysis and publication. This protocol is being transitioned to UCSD during year 3 of 5 from the University of Miami.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Essential tremor (ET) causes uncontrollable shaking, usually of the hands. Several medications are used to treat ET; however, they are often only partly effective and can have side effects that are not well tolerated. Many people with tremor have some relief from drinking alcohol. It is unclear however what brain areas produce tremors in ET and how these areas change during various activities or with medications that can suppress tremor. We plan to study the source of these tremors using functional magnetic resonance imaging (fMRI) and how tremor medications may impact the activity of various brain regions.

6. SPECIFIC AIMS

Essential Tremor (ET) is the most common tremor disorder, currently affecting an estimated 2.9 million Americans and leading to disability and decreased quality of life in 75% of cases. Tremor affects the arms disproportionately more than the head, legs, voice and face. ET may occur at any age, though prevalence increases after the age of 40. The pathophysiology of ET is poorly understood. The source of the tremor remains controversial since all studies show increased activity in the cerebellum (including mimicked tremor in controls), while animal models of ET using harmaline and a single human PET study implicate the inferior olivary nucleus in the brainstem. Treatment of ET focuses on pharmacological agents of various mechanisms (e.g. □-blockers, anticonvulsants, benzodiazepines) and rarely deep brain stimulation of the Vim thalamus. Despite the assortment of agents used to treat ET, only ~50% of patients benefit from a particular agent. Further, their mechanisms of action on tremor are not known and systemic adverse effects are common.

Our long-term goal is to improve treatment outcomes through the development of more focused therapies for ET, while minimizing adverse effects. The goal of this proposal is to identify the brain regions and networks associated with varying ET phenotypes and delineate the mechanisms by which treatment alters aberrant activity in these networks. ***The central hypothesis is that blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) correlates will identify the ET neural network along with mechanisms to***

regulate it. Our hypothesis was formulated based on our own preliminary data using established methods as well as a novel approach we have developed. Results obtained from the proposed study will provide the critical knowledge needed to pursue targeted drug and surgical development and ultimately improve treatment of ET.

Aim 1. Does the cerebellum have increased blood flow and functional connectivity at rest? We will collect functional MRI (fMRI) data while participants are at rest and not experiencing tremor. Accelerometry will be used to confirm that no tremors occurred during data acquisition. We will utilize our Context Differential Autocorrelation Mapping (CDAM) method to compare global functional connectivity in a group of subjects with ET to a group of age-matched controls. We hypothesize that the inferior olive, cerebellum, and red nucleus (Mollaret's triangle) will have significantly greater functional connectivity in the ET group compared with controls.

Aim 2. Are postural and kinetic tremors associated with different aberrant networks? We will collect fMRI data while ET subjects perform two separate tasks. During one task, subjects will be verbally cued to elevate their arm in a tonic position to manifest postural tremor during fMRI data acquisition, in a block-design paradigm. Accelerometry will be used to quantify the frequency and severity of the postural tremor. During a second task, subjects will be similarly cued to draw an Archimedes spiral to elicit kinetic tremor. Tablet drawings will be digitized to quantify the frequency and severity of the kinetic tremor. We will use established fMRI analysis methods to generate statistical parametric maps (SPMs) and CDAM to compare the regional differences in activation and connectivity between postural and kinetic tremor. We hypothesize that postural tremor will be associated with greater inferior olive activation and connectivity, while kinetic tremor will have greater cerebellar activation and connectivity.

Aim 3. What regulatory changes in the tremor networks occur to explain the tremor-suppression effects of ethanol and propranolol? Using the resting, postural, and kinetic paradigms in Aims 1 and 2, we will assess the fMRI-based activation and connectivity changes for all ET subjects under three conditions: baseline (no drug), acute ethanol (50ml of 40%EtOH) challenge, and stable dose of propranolol. We will assess the regional activation and functional connectivity responses for each condition using SPM and CDAM methods. We hypothesize that ethanol's mechanism of tremor suppression is by reduction of olivo-cerebellar connectivity, while propranolol acts to reduce inferior olive activation.

With respect to expected outcomes, the findings of aims 1-3 are expected to identify the neuroanatomical correlates of ET, with particular attention to the defining characteristics of postural and kinetic tremors of ET, and the underlying mechanisms of action on the structures identified of two existing agents with known efficacy. The knowledge gained by this work will have direct applicability to the development of: novel pharmacological agents and surgical devices with the aid of a neuroimaging biomarker. In addition, these findings stand to impact clinical management by providing information that can be used to tailor treatment to individual patient characteristics, thereby avoiding the trial-and-error methods currently used to guide agent selection (e.g. if □-blockers are found to act more effectively on a site associated with postural tremor). In addition, we plan to collect DNA samples on this rich dataset for future imaging-genomics studies.

7. BACKGROUND AND SIGNIFICANCE

Essential Tremor (ET) is the most common tremor disorder, currently affecting an estimated 2.9 million Americans and leading to disability and decreased quality of life in 75% of cases. Individuals with ET commonly experience tremors involving the arms that manifest during movement (kinetic tremors) or during sustained anti-gravity postures (postural tremors). This has a direct impact on the individual's ability to function in the workplace and/or perform their activities of daily living (e.g. eating, bathing). Diagnosis of ET is

commonly made based on consensus clinical criteria, and a history of alcohol- responsive tremors is highly suggestive of ET. Clinical management for moderate to severe cases begins with selection of a pharmacological agent with at least modest efficacy and favorable side effect profile, based on published treatment practice guidelines. Categories of centrally-active agents shown to have at least modest efficacy on ET include beta-blockers (e.g. propranolol), antiepileptics (e.g. primidone, topiramate), and benzodiazepines (e.g. clonazepam). Despite the seeming diversity of agents for ET, 25- 55% of patients gain no benefit and side effects are common and may limit long-term use. Furthermore, there appears to be a dissociation of tremor subtypes, with some patients showing greater improvement in one subtype of tremor than the other, though this has not been rigorously studied. The proposed work seeks to address many of these current barriers to progress in ET research including: 1) limited knowledge of the brain regions generating ET; 2) unknown and possibly independent mechanisms for postural and kinetic tremors; and 3) unknown mechanism of action of various agents on the tremor network(s). Using a non-invasive method like fMRI to study the whole brain, we aim to further characterize the ET neural network(s), determine whether postural and kinetic tremors are associated with different neural networks, and elucidate the mechanism of action of two pharmacological agents on the ET neural network(s). Knowledge gained from this study will have a direct impact on the development of targeted agents with less systemic adverse effects and will provide additional knowledge about the phenotypic variability of ET. Ultimately, this will potentially lead to more patient-specific treatment algorithms and will improve quality of life for patients with ET.

8. PROGRESS REPORT

1. Our recruitment efforts have been maintained during the past year. In addition to enrollment from Dr. Nahab's clinic, we are receiving numerous inquiries from potential participants who find this project listed on the International Essential Tremor Foundation (IETF), Tremor Action Network, and HopeNET websites. In addition, the IETF organized a number of ET information events across the country. Dr. Nahab and/or the study coordinator attended meetings in Boca Raton, Miami, and Tampa, Florida with study-related materials and information to minimize the complexity of travel to Miami. In addition, a number of individuals have personally flown to Miami to participate from Nevada, Georgia, and even South America. To date, we enrolled 22 subjects with Essential tremor and 8 matched controls for a total of 30 subjects from the University of Miami, 27 of which have completed their participation. Three subjects did not complete the study. One ET subject withdrew prior to MRI due to a new serious medical condition that took precedence over participating in study. Another ET subject was "lost to follow-up" and the third control subject did not complete due to experiencing claustrophobia just prior to starting MRI. We have no adverse events to report and no subject receiving alcohol experienced intoxication based on both clinical assessment and the use of the standardized Alcohol Intoxication Scale. Of those subjects who were enrolled on tremor medications, all were able to safely taper off of their medications with an expected worsening of their tremors. Since we plan to collect up to 55 ET subjects and 33 matched controls over the life of the grant, we continue to allow for a slight lag in the collection of the controls to ensure we collect subjects well---matched to our ET subject group and since the recruitment of controls is likely to be a simpler process.

2. Recruitment efforts for the upcoming year in San Diego will maintain collaborations with the various national and international tremor foundations. In addition, subjects will be enrolled from the UCSD Movement Disorders Center and the surrounding community. We continue to anticipate no problems in recruiting the sample size proposed.

3. Data analysis has been proceeding on the numerous datasets collected in this proposal, including clinical rating scales (MDS-UPDRS, TETRAS, MoCA, etc.), spirography data, accelerometry, and the diverse set of imaging (3D-T1, arterial spin labeling, fMRI, diffusion tensor imaging, etc.). An extensive amount of time has been spent trying to optimize the pre---processing algorithms of the respective data types in order to improve sensitivity and specificity. Since the sample sizes remain well below our numbers needed to test our

hypotheses, we have not performed any formal analyses. Nonetheless, we are currently at a point where we can evaluate the efficacy of our tasks at producing activation patterns in expected motor related brain regions and those group analyses are currently underway.

4. Preliminary Results: Here we provide a representative sample of data taken from a subject with ET (P08). Analysis of the fMRI data was performed on the baseline spirography task that is designed to elicit kinetic tremor (see Figure 1).

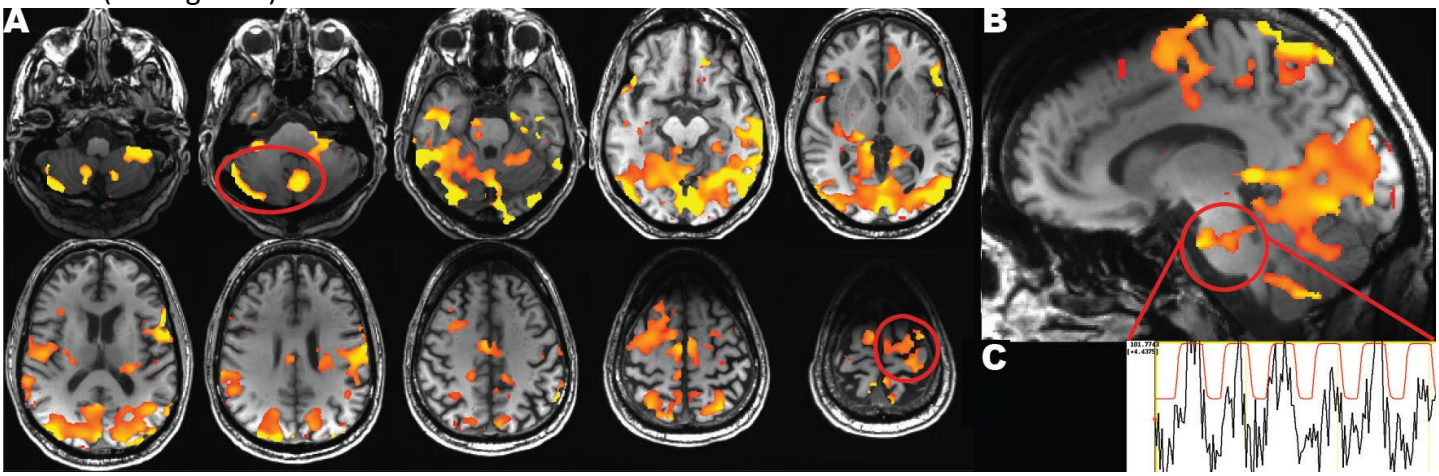

Figure 1: Statistical parametric map of brain regions showing task---correlated BOLD responses during a spirography task in 1 subject with Essential Tremor. A) Axial fMRI shows areas of task---correlated response ($p<10^{-13}$), with left primary motor cortex and right cerebellum (circled). B) Sagittal fMRI demonstrating midline activations and a pontine activation (circled) showing a highly task---correlated hemodynamic responsive seen in C) with the subject responsive shown in black and the stimulus paradigm overlaid in red. NOTE: The broad activation patterns are expected since this task also requires visual input. We do not anticipate visual areas will, however, be modulated by tremor severity across our population once that covariate is introduced into the analysis.

Publications:

There have been no direct peer-reviewed publications related to the specific aims. Several relevant manuscripts were published by the PI during this award period and are included in eSNAP. These peer-reviewed manuscripts provide the rationale and validation for the methods employed in this research proposal.

9. RESEARCH DESIGN AND METHODS

The study population will include patients diagnosed with essential tremor (ET) and healthy volunteers without a major neurological disorder based on inclusion/exclusion criteria described in section 10. All subjects will be recruited nationally with the aid of ET foundations and support groups, locally, and from the movement disorder clinic at UCSD. Every potential subject expressing interest in participating will undergo a telephone pre-screening to ensure they fulfill inclusion-exclusion criteria before being invited for the formal evaluation (screening visit). In order to balance the ethical conflicts of clinician and researcher, all potential participants will be provided with the informed consent form beforehand to review with their loved ones, thus eliminating the pressure to decide immediately whether to participate in study. Informed consent will be discussed with the subject by the study team. The informed consent phase will engage not only the subject but also the family members and/or friends and everyone involved is given the opportunity to ask questions and address concerns. Subjects providing informed consent will then be enrolled into the study.

Healthy Volunteer Study Procedures

SCREENING

After being screened for eligibility and providing informed consent, volunteers will have a thorough

examination that will lasts approximately 2-hours. PI will obtain medical history, and a videotaped neurological exam that includes the following assessments: United Parkinson's Disease Rating Scale (UPDRS), Essential Tremor Rating Assessment (TETRAS), Montreal Cognitive Assessment (MOCA), Scale for the Assessment and Rating of Ataxia (SARA), baseline Spirography and Accelerometry. If PI finds any non-ET abnormalities during the evaluation, the subject will be excluded and advised to consult their personal physician.

VIDEO RECORDING

As part of the evaluation, a video recording will be collected to document exam findings. Participants decide whether these videos may be used solely by the research team for this research project, or additionally may be used for other purposes such as educational or scientific meetings.

BLOOD SPECIMEN COLLECTION

As a part of the screening visit, participants will be asked permission to collect a blood sample that will be used as a control for future genetic research on ET and related disorders. The total amount of blood removed will not exceed 20 ml (4 teaspoons).

FUNCTIONAL MRI (FMRI)

After completion of the screening visit, subjects will be scheduled for the fMRI visit that will last no more than 2-hours. Subjects will be asked to lie still for up to 15 minutes at a time. An accelerometer device will be placed on the hand to measure movement. We will use fMRI to observe the brain's activity during three (3) different activities: arms resting by the side, right arm elevated and maintained in the air, and while drawing a spiral with the right hand. These tasks will be performed multiple times during 5-minute runs.

At the completion of study participation, subjects will receive payment for their participation. Payments for incomplete participation will be prorated based on consent form guidelines.

ET Volunteer Study Procedures

SCREENING

Subjects will be screened for eligibility and after providing informed consent, PI will conduct an examination to confirm the diagnosis of Essential Tremor (ET) and to exclude any other neurologic disorder. PI will obtain medical history, and a videotaped neurological exam that will include the following assessments: United Parkinson's Disease Rating Scale (UPDRS), Essential Tremor Rating Assessment (TETRAS), Montreal Cognitive Assessment (MOCA), Scale for the Assessment and Rating of Ataxia (SARA), baseline Spirography and Accelerometry. A urine pregnancy test will be performed on female participants of childbearing potential.

VIDEO RECORDING

As part of the evaluation, a video recording will be collected to document exam findings. Participants decide whether these videos may be used solely by the research team for this research project, or additionally may be used for other purposes such as educational or scientific meetings.

BLOOD SPECIMEN COLLECTION

As a part of the screening visit, participants will be requested to provide a blood sample that will be used for future genetic research on ET and related disorders. The total amount of blood removed will not exceed 20 ml (4 teaspoons).

MEDICATION TAPER

A tremor medication consultation will be conducted with the PI reviewing the medication history. Participants taking no medications for ET will proceed to be randomized to one of the two fMRI visits (A or B). If a subject is on tremor medications and gives consent to participate in this study, tremor medications will need to be discontinued. This plan may be carried out by either the subject's primary physician or study PI in consultation with the Safety Advisory Committee (see section 14), depending on preference of subject and

treating physician. If subject has a treating physician, the PI will contact the physician to discuss whether there are any potential safety concerns with tapering tremor medications and review the plan to taper/titrate medications; taper will only occur with physician approval. The duration of the medication taper prior to MRI visit A depends on the type of tremor medication the subject is on with the period being at least five half-lives. In terms of the period between MRIs, this may be as short as two weeks and up to several months, though no explicit time limitations are set. The duration depends upon the time needed for a subject to taper off all tremor medications for MRI visit A, and the time necessary to reach a steady state of propranolol SR for MRI visit B. If a subject cannot tolerate the medication taper (e.g. worsening tremors create undo disability or the presence of an unexpected adverse effect), the PI will consult with the Safety Advisory Committee and discuss restarting medications with subject and treating physician (if present) and subject will be withdrawn from the study.

FUNCTIONAL MRI (FMRI) OVERVIEW

After completion of the screening visit, subjects will be scheduled for the fMRI visit that will also last approximately 2-hours. Women of childbearing potential will undergo a second urine pregnancy test prior to MRI visit A. ET participants already on stable doses of Propranolol SR will first undergo fMRI on Propranolol SR. Participants taking no medications for ET will be randomized to one of the two fMRI visits (A or B). After completion of one, participants will undergo the other visit type.

FMRI VISIT A

During this visit, subjects will remain off tremor medications for a set period of time. The PI will provide specific instructions about how to do this since it varies based on the individual subject's medication history. Women of childbearing potential will undergo a second urine pregnancy test prior to MRI. During this visit, subject will be asked to perform three different activities: arms resting by the side, right arm elevated and maintained in the air, and while drawing a spiral with the right hand. Subject will perform these tasks multiple times during 5-minute runs. PI will then provide subject with a single 50-ml serving (1 shot) of 40% ethanol to drink and a high resolution structural MRI is performed, during which time the tremor suppression effects will begin. The same tasks performed during the first half of the study will be repeated. PI will complete an Alcohol intoxication Scale at the onset of the visit and again after MRI to ensure subjects are not intoxicated upon discharge. Subjects who demonstrate signs of intoxication will be monitored until they are back to their baselines.

FMRI VISIT B

During this visit, we will study how the brain and tremors respond to propranolol SR (Inderal LA). Before participating in this visit, subjects will need to be on a stable dose of this medication. In order to accomplish this, the subject will receive detailed instructions from PI on how to start and increase the medicine in consultation with the treating physician and/or Safety Advisory Committee. Subject responses to medication (benefits and adverse effects) will be monitored through weekly telephone calls. Once a stable dose of medication has been achieved, the subject will be scheduled for the fMRI scan. During this visit, the subject will be asked to perform three different activities: arms resting by the side, right arm elevated and maintained in the air, and while drawing a spiral with the right hand. At the completion of the visit, the study investigator will instruct the subject on how to taper off this medicine based on consultation with the treating physician and/or Safety Advisory Committee.

STUDY COMPLETION

Three (3) scenarios exist for study completion/termination:

1) Premature termination prior to completion of all visits

In this scenario, the subject will return to their baseline medications under the direction of their treating

physician and/or PI in consultation with the Safety Advisory Committee. Payments for incomplete participation will be prorated based on consent form guidelines.
2) *Subject who was not initially on tremor medications completes the study.* PI will discuss with the subject whether they wish to return to being on no medications or whether they wish to remain on propranolol SR. If no medications are requested, PI will guide/assist with tapering schedule in consultation with the treating physician and/or Safety Advisory Committee. If subject wishes to stay on propranolol SR, PI will assist or coordinate with primary treating physician to keep subject on the medication after the completion of the study at the subject's expense. Subject will receive payment for study completion.
3) *Subjects who were on tremor medication(s) at start of the study.* The PI will confirm with subject their desire to restart their tremor medications. PI will guide/assist with titration schedule in consultation with the treating physician and/or Safety Advisory Committee. Subject will receive payment for study completion.

10. HUMAN SUBJECTS

Population:
88 volunteers (Age 21 or over) will participate in this study. This includes a total of 55 ET subjects and 33 matched controls. Of these, 27 subjects have already completed participation and were enrolled at the University of Miami. Thus, 61 additional subjects will be enrolled at UCSD. Participants will be selected without regard to ethnicity or race.

Inclusion Criteria ET Patients:

- Age 21 or over
- Subjects willing to abstain from caffeine or alcohol for 48 hours prior to the fMRI scanning
- Diagnosis of Essential Tremor by a Movement Disorder specialist based on Tremor Research Group criteria

Age-matched Controls:

- Age 21 or over
- Absence of a primary neurological diagnosis

Exclusion criteria All Subjects:

- Abnormal findings on neurological exam consistent with an organic disorder
- Presence of a resting tremor on exam
- Pregnant, nursing, or suspected pregnancy
- Finding on the MRI safety questionnaire contraindicating MRI
- History of dementia, brain tumor, stroke, head trauma or a vascular malformation as obtained by history or from imaging studies
- History of a severe medical condition, such as cardiovascular disease, preventing subject from lying flat for up to 120 minutes
- Lacking the capacity to provide informed consent
- Claustrophobia or other restrictions that prevent subject from undergoing a scan in a confined space for up to 120 minutes
- Acute or chronic medications that influence hepatic metabolism or CNS function and cannot be temporarily discontinued for the length of the study
- Use of beta blocker medications for the management of hypertension

ET Patients:

- Movement frequency and severity preventing safe and effective MRI data collection
- Active or prior history of alcohol abuse or dependence
- Subject unwillingness to take a potentially intoxicating drug (ethanol)

- You do not have an accompanying adult who can provide transportation for you after consuming alcohol during one of the MRI visits
- You have an allergy to alcohol (ethanol)
- History of deep brain stimulation surgery or thalamotomy

Age-matched Controls:

- Use of a medication known to have tremor effects that cannot be temporarily tapered and discontinued (see below).

List of Medications with Known Tremor Activity:

Benzodiazepines (any)
Beta-blockers (any)
Carbemazepine
Gapapentin
Levetiracetam
Oxybate
Phenytoin
Primidone
Topiramate
Valproic acid
Zonisamide

PI will rely on self-reporting for inclusion/exclusion criteria. If PI has validity questions after informed consent is provided during the screening visit, medical records will be requested for further review.

11. RECRUITMENT

Multiple methods will be employed to recruit subjects into this study, including direct enrollment by the PI. We anticipate referrals from other faculty members in the division of movement disorders at UCSD. In addition, we will recruit through, local community outreach (performed by PI and study coordinator), and national outreach through the various tremor foundations and support groups. We intend to use ResearchMatch to contact prospective participants. The proposed recruitment message is included in a separate page labeled, "ResearchMatch Message to Potential Participants." Additional recruitment methods that may be employed include: flyers/posters, web postings, contact letters to physicians and clinics, and newspaper ads which will be submitted to the IRB for approval prior to use.

12. INFORMED CONSENT

Subjects that have shown interest to participate in this study will be contacted by phone and will be asked to give verbal consent for the researcher to write down contact details and the answers to a few screening questions related to health and MRI safety. This screening presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context, which justifies obtaining a verbal consent. Subjects who are eligible based on this pre-screen will be scheduled for a formal screening visit where documented informed consent will be obtained.

13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative is not to participate in this study. Subjects can decide to stop participating at any time without affecting medical care.

14. POTENTIAL RISKS

RISK OF MRI
The major risks and discomforts of this study are those associated with MRI scanning. People are at risk for

injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. We will utilize standard clinical screening methods employed by the department of Radiology to identify such conditions prior to the study. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) will be removed before entering the MRI scan room based on UCSD standard operating procedures. Women who are pregnant will not participate in this study. Individuals with fear of confined spaces who may become anxious during an MRI will be excluded. Otherwise, there are no known long-term risks or consequences of MRI scans. Incidental findings of pathology noted on MRIs will be reported to the study participant and they will be advised to obtain clinical follow up with their primary physician for further testing/management.

RISK OF DISCONTINUATION OF MEDICATIONS

This study requires subjects with ET to discontinue tremor medications prior to certain imaging visits. This may result in temporary worsening of tremor. All adjustments and recommendations with regard to medications will be carried out at the discretion of and in concert with the subject's treating physician with safety being the highest concern. No safety concerns are associated with the slow taper off tremor suppressing medications, but subjects will be informed by the PI and through the Informed Consent that their tremors may transiently worsen. If a subject cannot tolerate medication discontinuation (e.g. worsening tremors create undo disability or another unexpected adverse effect), the PI will discuss restarting medications with subject and treating physician (if present) and subject will be withdrawn from the study. It should be noted that this scenario is unlikely, since the efficacy of all tremor medications currently FDA-approved are modest at best. In addition, an independent Safety Advisory Committee comprised of movement disorders specialists (e.g. Drs. Stephanie Lessig, Irene Litvan and David Song) will meet with the PI on a monthly basis to review medication changes and safety concerns associated with the study. No explicit stopping rules are set, since the driving force of stopping a medication will be the subjects themselves. In the case that the PI is also the subject's primary treating physician, he will document conferring with the Safety Advisory Committee. Subjects will be informed of these risks in the consent and told that the tremors will improve once medication is restarted at the completion of the study. It is always the subject's right to withdraw from the study at any time prior to completion. The PI also reserves the right to exclude or withdraw subjects from the study if participation poses a safety risk.

RISK OF ALCOHOL

As a part of the fMRI study, there is a risk of intoxication associated with the use of alcohol. To minimize this potential risk, subjects will receive a single serving of alcohol (40% Ethanol by volume). The study team will monitor subjects for intoxication during the entire scan session. To further minimize risk, subjects will undergo an intoxication evaluation before and after the study visit by a study investigator to confirm the subject can leave safely. If subjects show signs of intoxication, the study team will monitor them until all signs of intoxication have resolved. Additionally, subjects are required to have an accompanying adult who will provide transportation.

RISK OF GENETIC TESTING

As a part of this proposal, we intend to collect DNA samples for the purpose of future imaging genomics research. No analysis will take place during this proposal and samples will simply be collected, processed and stored for future study. Assuming future analysis and use of this data, there is a theoretical risk for

discrimination towards individuals who are at risk for a medical disorder or have a medical disorder/condition in their family. Potential discrimination may include barriers to insurability, employability, or other unidentified adverse effects. Extensive efforts are made to protect all research subjects from prejudice, discrimination, or uses of this information that will adversely affect them.

In the event of further research studies of this genetic information, no results will be provided to participants. However, any significant new findings developed during the course of this research that may bear upon the participants' condition or their willingness to continue participation in the research will be provided. It is possible that future studies will identify information about the participant that was previously unknown (disease status or risk, non-paternity). Such incidental findings, if any, will not be shared with the participant or the participant's relatives unless the incidental finding will significantly impact health outcomes or reproductive choices for the participant and/or his/her immediate family. This determination will be made on a case by case basis by the PI with guidance from the UCSD Institutional Review Board. Such incidental findings will not be shared with anyone related to the participant unless the incidental finding is life threatening. Cells, tissue, blood, tumor tissue, or other biological specimens removed from the participant during the course of this study may be valuable for scientific, research, or teaching purposes, or for the development of a new medical product. These samples are unavailable for clinical (diagnostic) purposes and any future diagnostic testing as a result of this or other research must be performed on a new sample. Risks associated with participation in this study also include the minor risks associated with venipuncture to obtain blood for DNA, such as bruising or fainting.

RISKS OF PROPRANOLOL SR (INDERAL SR)
Use of this medication during the study is anticipated to improve tremors. Not all individuals will experience a reduction in their tremors. Although this study excludes any individuals with known contraindications to this medication from participating, they may experience additional side effects. The most common side effects include: fatigue, dizziness, constipation, slow heart rate, low blood pressure, depression, insomnia, weakness, disorientation, nausea, diarrhea, allergic reaction, bruising, hair loss, and impotence. Serious side effects include: heart failure, severe slowing of heart rate or heart block, bronchospasm, lupus, severe rash, or anaphylaxis. This medication is approved for the treatment of Essential Tremor.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

RISK OF MRI SCANNING

In this project, a 3 Tesla (3T) MRI scanner will be used. Such magnetic fields are within the guidelines provided by the IEC (International Electro technical Commission, Europe) and the FDA (Food and Drug Administration, USA) for clinical imaging and fall within the category of no significant risk. Screening of the subjects for MRI safety will take place at three different time points: before inclusion into the study, at the start of a test day, and right before they go into the scanner.

- Metal objects: Participants and all other people who want to enter the scanner room will be carefully screened for metal objects. Someone with non-removable metal objects is not allowed in the scanner room, participants with non-removable metal objects will not be included in this study. If there is any doubt about the nature of implanted material, participants will not be scanned. In addition, it will be ensured that no ferromagnetic objects are in the vicinity of the MRI scanner.
- Medical devices: Participants with non-removable medical devices that might become dysfunctional because of MRI scanning will not be included in this study.
- Burn wounds: Participants will be carefully screened for anything that could increase the risk of burns. Participants with tattoos, permanent make-up or a chance of having metal parts in their eyes will not be included in this study. When participants are placed on the scanning table, special care will be

given to the placing of cables.

- Scanner noise: All participants will wear earplugs and sound-attenuating headphones.
- Incidental findings: When abnormalities are spotted on the MRI images, the images will be shown to a neuroradiologist working at the UCSD. If the radiologist agrees that there is a significant abnormality on the MRI image, the researcher will inform the participant. With the permission of the participant a follow-up meeting will be arranged with the participant's primary physician and/or UCSD Radiology (depending on the recommendation of the reviewing radiologist).

RISK OF DISCONTINUATION OF MEDICATIONS

This study requires subjects with ET to discontinue tremor medications prior to certain imaging visits. This may result in temporary worsening of tremor. If a subject cannot tolerate the medication discontinuation (e.g. worsening tremors create undo disability), the PI will discuss restarting medications with the subject, treating physician (if present), and or Safety Advisory Committee and the subject will be withdrawn from the study. It should be noted that this scenario is unlikely, since the efficacy of all tremor medications currently FDA-approved are modest at best. No explicit stopping rules are set, since the driving force of stopping a medication will be the subjects themselves. No safety concerns are associated with the slow taper off tremor suppressing medications, but subjects will be informed by the PI and through the Informed Consent that their tremors may transiently worsen. In the case that the PI is also the subject's primary treating physician, he will document conferring with the Safety Advisory Committee (see section 14, Risks of Medication Discontinuation). Subjects are informed of these risks in the informed consent. It is always the subject's right to withdraw from the study at any time prior to completion. The PI also reserves the right to exclude or withdraw subjects from the study if participation is not in their best interest

RISK OF ALCOHOL

As a part of the fMRI study, there is a risk of intoxication associated with the use of alcohol. To minimize this potential risk, subjects will receive only a single serving of alcohol (40% Ethanol by volume). The study team will monitor subjects for intoxication during the entire scan session. To further minimize risk, subjects will undergo an intoxication evaluation before and after the study visit by a study investigator to confirm the subject can leave safely. If subjects show signs of intoxication, the study team will monitor them until all signs of intoxication have resolved. Additionally, subjects are required to have an accompanying adult who will provide transportation.

RISK OF GENETIC TESTING

As a part of this proposal, we intend to collect DNA samples for the purpose of future imaging genomics research. No analysis will take place during this proposal and samples will simply be collected, processed and stored for future study. Assuming future analysis and use of this data, there is a theoretical risk for discrimination towards individuals who are at risk for a medical disorder or have a medical disorder/condition in their family. Potential discrimination may include barriers to insurability, employability, or other unidentified adverse effects. Extensive efforts are made to protect all research subjects from prejudice, discrimination, or uses of this information that will adversely affect them. In the event of further research studies of this genetic information, no results will be provided to participants. However, any significant new findings developed during the course of this research that may bear upon the participants' condition or their willingness to continue participation in the research will be provided. It is possible that future studies will identify information about the participant that was previously unknown (disease status or risk, non-paternity). Such incidental findings, if any, will not be shared with the participant or the participant's relatives unless the incidental finding will significantly impact health outcomes or reproductive choices for the participant and/or his/her immediate family. This determination will be made on a case by case basis by the PI with guidance from the University of California San Diego Institutional Review Board. Such incidental findings will not be shared with anyone related to the participant unless the incidental finding is life threatening. Cells, tissue,

blood, tumor tissue, or other biological specimens removed from the participant during the course of this study may be valuable for scientific, research, or teaching purposes, or for the development of a new medical product. These samples are unavailable for clinical (diagnostic) purposes and any future diagnostic testing as a result of this or other research must be performed on a new sample. Risks associated with participation in this study also include the minor risks associated with venipuncture to obtain blood for DNA, such as bruising or fainting.

RISKS OF PROPRANOLOL SR (INDERAL SR)

Use of this medication during the study is anticipated to improve tremors. Not all individuals will experience a reduction in their tremors. Although this study excludes any individuals with known contraindications to this medication from participating, they may experience additional side effects. The most common side effects include: fatigue, dizziness, constipation, slow heart rate, low blood pressure, depression, insomnia, weakness, disorientation, nausea, diarrhea, allergic reaction, bruising, hair loss, and impotence. Serious side effects include: heart failure, severe slowing of heart rate or heart block, bronchospasm, lupus, severe rash, or anaphylaxis. This medication is approved for the treatment of Essential Tremor. Participants will be encouraged to report any concerns to the physician, who will be available 24 hours a days, 7 days a week, by cell phone/voice mail. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be registered. All adverse events will be followed up until they have abated, or until a stable situation has been reached.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

We have instituted numerous precautions to protect the confidentiality of the data we obtain. Data on each subject will be recorded in a computer database with an individual study ID number. All identifiers such as name, address, and telephone number will be kept in a separate data file from the subject data. The files can only be accessed through a specific UCSD computer account protected by a password. Computer access is based on regulations maintained by the UCSD Administrative Computing and Telecommunications department (ACT). All study information will be stored in locked file cabinets inside a locked office, and only study personnel will have access to the identifying data. Subject identity will not be disclosed to any person, except in the event of a medical emergency or if required by law. Distributed data sets for statistical analyses will not include any of the key personal identifiers and will be linked only by the unique study IDs.

17. POTENTIAL BENEFITS

Although there is no direct benefit of this research to the participants, the information generated as part of this proposal may help us to better understand the physiology of essential tremor.

18. RISK/BENEFIT RATIO

The potential findings of this work may provide a better understanding of the brain structures and mechanisms that lead to ET, but also help to understand the mechanisms underlying treatment response that are currently poorly understood. This has the potential to lead to a better understanding of the disease and also to future treatments that are more targeted toward the structures involved. While there is a minimal risk to the use of Inderal LA or alcohol during this study, these are both well studied agents and Inderal LA is approved for clinical management of ET. Neither agent is therefore likely to represent greater than minimal risk. There is no anticipation that genetic testing obtained in this study will detect any known genetic disease.

19. EXPENSE TO PARTICIPANT

The only expense to the participant is medication related. At least 30% of ET subjects enrolled into this study are already taking Inderal LA or the equivalent Propranolol SR. We have evaluated the viability of supplying all participants with study-sponsored drug but that solution was not financially viable. Some of the individuals coming into the study may be on the brandname Inderal LA while others may be on the generic Propranolol SR. The cost of the brandname is prohibitive and these added costs were not budgeted nor approved by NIH.

Additionally, it would be unethical to switch formulations on a patient who is comfortably taking the brand name because it would be cost effective to us. Therefore, the most viable option would be to have subjects purchase the medication, brand or generic, retain their receipts and provide them to the study coordinator. We will reasonably reimburse subjects for the cost of their medication.

20. COMPENSATION FOR PARTICIPATION

ET subjects will receive up to $150 for completing this study. If study is not completed, payment will be pro-rated based on the following schedule:

$50 Signing Informed Consent and Completion of Screening Visit
$50 Functional MRI Visit A Completion
$50 Functional MRI Visit B Completion

Healthy Volunteers will receive up to $100 for completing this study. If study is not completed, payment will be pro-rated based on the following schedule:

$50 Signing Informed Consent and Completion of Screening Visit
$50 Functional MRI Visit Completion

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Dr. Nahab is an M.D. and is Associate Professor of Neurosciences at UCSD. He serves as Principal Investigator of this study. His responsibilities will include supervision of all aspects of this study, subject screenings, assisting with data collection, data analysis, and reporting of the study results. Dr. Nahab has medical privileges at UC Medical Centers the CTRI.

Dr. Shen is a Ph.D. and is Assistant Research Project Scientist in the department of Neurosciences at UCSD. She serves as a co-investigator on this study. Her responsibilities include assisting with experimental design and implementation, data collection, data analysis and assisting with reporting of the study results.

Ms. Moreno serves as a Research Coordinator in Dr. Nahab's Functional Imaging of Neurodegenerative Disorders Lab in the department of Neurosciences at UCSD. Her primary responsibilities will include subject enrollment, and data management.

All of the above personnel are being funded in part by this NIH grant and have completed the appropriate CITI training with completion reports available for review upon request.

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Grant number: 1R01NS073683-01A1

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable

26. IMPACT ON STAFF

Nurses from the UCSD Clinical and Translational Research Institute (CTRI) will assist in this study. They will, measure blood pressure, heart rate and take a DNA blood sample to be stored for genetics (30 min in total). The impact on the nursing staff is in total 30 hrs.

27. CONFLICT OF INTEREST

There are no conflicts of interest to declare.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

No decisionally impaired individuals will be studied in this protocol.